UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,609	12/28/2000	David Robertson	1242/27/2/2	6747

25297 7590 01/02/2003

JENKINS & WILSON, PA
3100 TOWER BLVD
SUITE 1400
DURHAM, NC 27707

EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 01/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,609	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *18-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,9-13,16 and 17* is/are rejected.

7)☒ Claim(s) *4-5, 8,14-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of claims 1-17 in Group I in Paper No. 9 is acknowledged.

2. Claims 1-17 are considered for examination in this office action. Claims 18-79 are withdrawn from further consideration.

3. The Information Disclosure Statement (Paper NO. 2) filed on May 18, 2001 has been entered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 recites the limitation "polypeptide" in NE transporter nucleic acid. There is insufficient antecedent basis for this limitation in the claim because the instant claim 4 depends on claim 3, which recites a nucleic acid and not a polypeptide. Amendment of the claim to recite 'nucleic acid' would obviate the rejection.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1-3, 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Flattem et al. (Am J Human Genetics, Vol. 65, No.4, pp. A43, 1999).

Flattem et al. teach a method for screening for susceptibility to norepinephrine (NE) transporter in a human subject wherein Flattem et al. teach that the method comprises (a) obtaining a biological sample from a human subject (proband) and detecting a polymorphism

(mutation) of a norepinephrine (NE) transporter in the biological sample from the subject and detecting the presence of the polymorphism (mutation) as an indication of the susceptibility of the subject to a sub-optimal NE transport in orthostatic intolerance (see page A43, abstract No. 223). Thus the disclosure of Flattem et al. meets the limitations in the instant claims.

B. Claims 1, 3, 6-7, 13, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998).

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1). Thus the disclosure of Jonnsson et al. meets the limitations in the instant claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998) in view of Jacob et al. (Circulation, Vol. 99, pp. 1706-1712, 1999).

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jaonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1). However, Jonnsson et al. did not teach correlation of sub-optimal NE transport to orthostatic intolerance.

Jacob et al. teach a method for screening for susceptibility to sub-optimal nor epinephrine (NE) transport in a human subject wherein Jacob et al. teach that the method comprises (a) obtaining a biological sample from the subject (see page 1707, column 2, paragraph 1); and detecting sup-optimal nor epinephrine in the biological sample as an indication of susceptibility to NE transport (see page 1707, column 2, paragraphs 2-4, page 1708, column 2, paragraph 2).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of detecting polymorphism in NE

transporter as taught by Jonnsson et al. with determining abnormal norepinephrine clearance in orthostatic intolerance as taught by Jacob et al. to achieve expected advantage of developing a sensitive method for detecting susceptibility of a subject to orthosatic intolerance (OI) because Jacob et al. suggests that "impairment in the norepinephrine transporter colud be responsible for the decreased norepinephrine spillover observed in the OI patients and the role of norepinephrine transporter function in the dramatic abnormalities in catecholamine clearance must receive increased attention" (see page 1710, column 2, paragraph 1, and page1711, column 2, paragraph 3). An ordinary practitioner would have been motivated to combine the method of Jonnsson et al. with the method of Jacob et al. to improve the sensitivity of the assay by incorporating the additional parameters (such as correlating the polymorphism in NE transporter gene to susceptibility to OI) because this limitation would improve analysis, which would result in a better detection of orthostatic intolerance in human subjects.

B. Claims 11-12, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998) in view of Pesonen et al. (6,013,449).

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of

polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1). However, Jonnsson et al. did not teach detection of polymorphism using dideoxy sequencing reaction.

Pesonen et al. teach a method for detecting a polymorphic allele of serotonin receptor wherein Pesonen et al. discloses that the method comprises amplification of target DNA using polymerase chain reaction and detection of polymorphic allele using dideoxy cycle-sequencing (see column 5, lines 24-67, column 6, lines 1-29). Pesonen et al. also teach that the method comprises polypeptide sample (see column 3, lines 4-46).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining polymorphism as taught by Jonnsson et al. with the method of detecting variants by sequencing as taught by Pesonen et al. to achieve expected advantage of developing a sensitive method for detecting site of polymorphism of NE transporter gene in a human subject because Pesonen et al. suggests that "sequencing reactions of amplified PCR fragments provide determination of carriers of the variants (see column 6, lines 13-17). An ordinary practitioner would have been motivated to combine the method of Jonnsson et al. with the method of Pesonen et al. to improve the sensitivity of the assay by incorporating sequencing because this limitation would improve analysis, which would result in a better characterization of the polymorphism.

C. Claims 9-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998) in view of Weimer et al. (USPN. 6,248,526).

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jaonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1). However, Jonnsson et al. did not teach use of different labels on the two PCR primers.

Weimer teaches a method for detecting a target nucleic acid using labeled primers wherein, Weimer discloses that the method comprises (i) labeling of first (forward) or second (reverse) primer or both primers (see column 3, lines 13-19); (ii) labels include enzymes and enzyme substrates, radioactive atoms, fluorescent dyes, chromophores (see column 3, lines 35-47) which may be combined to achieve a desired effect, such as one might label a primer with biotin and detect the presence of the primer with avidin labeled with ^{125}I (see column 3. lines 57-67, column 4, lines 1-2).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining polymorphism as taught by Jonnsson et al. with the method of detecting target nucleic acid using labeled primers as

taught by Weimer to achieve expected advantage of developing a sensitive method for detecting site of polymorphism of NE transporter gene in a human subject because Weimer et al. suggests that "the use of labeled primers increases fluorescence signal which is directly proportional to the quantity of amplified DNA. An ordinary practitioner would have been motivated to combine the method of Jonnsson et al. with the method of Weimer to improve the sensitivity of the assay by incorporating the labeled primers because this limitation would improve analysis, which would result in a better characterization of the target polymorphism.

Allowable Subject Matter

7. Claims 4-5, 8, 14-15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The claims are allowable if rewritten in the independent form because these claims are free of art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-305-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
December 23, 2002

JEFFREY SIEW
PRIMARY EXAMINER
12/23/02